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Treatment of Children With Stage IV Favorable Histology Wilms Tumor: A Report From the National Wilms Tumor Study Group

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The purpose of this study was to evaluate the effect of the sequential addition of doxorubicin and cyclophosphamide to the combination of vincristine and actinomycin D on the relapse-free survival of children with stage IV/favorable histology Wilms tumor. We reviewed the clinical courses of all randomized patients from National Wilms Tumor Study (NWTS)-2 and 3 with stage IV/favorable histology (FH) Wilms tumor. We determined the four-year relapse-free survival percentage for patients treated on NWTS-2 with the combination of vincristine (VCR) and actinomycin D (AMD) with (regimen D) or without (regimen C) doxorubicin (DOX), and for patients treated on NWTS-3 with the combination of VCR + AMD + DOX with (regimen J) or without (regimen DD-RT) cyclophosphamide (CTX). All children received whole lung radiation therapy.

The four-year relapse-free survival percentage for children with stage IV/FH Wilms tumor treated with regimen C was 53.3%, compared to 57.7% for those treated with regimen D ($P = 0.63$). The four-year relapse-free survival percentage for children with stage IV/FH Wilms tumor treated with regimen DD-RT was 79.0%, compared to 80.9% for those treated on regimen J ($P = 0.79$). The four-year relapse-free survival for children with lung metastases only treated with regimen D on NWTS-2 was significantly lower than that of children treated with the related regimen DD-RT on NWTS-3 ($P = 0.03$).

We conclude that the addition of doxorubicin to the combination of vincristine and actinomycin D and pulmonary irradiation did not clearly improve the four-year relapse-free survival percentage of children with stage IV/FH Wilms tumor, although the benefit may have been masked by the greater frequency of death due to toxicity in NWTS-2. There was no evidence that the addition of CTX to the three-drug treatment regimen improved the four-year relapse-free survival percentage of children with stage IV/FH Wilms tumor. The data with only two drugs derived from NWTS-2 suggest that there is a population of children with stage IV/FH Wilms tumor who can be successfully treated without an anthracycline. The goal of future research will be to identify this subgroup at the time of initial diagnosis.

Key words: Wilms tumor; neoplasm, metastasis; neoplasm, radiotherapy; doxorubicin; actinomycin D; vincristine; cyclophosphamide

INTRODUCTION

The treatment of children with Wilms tumor is very successful. More than 80% of children with unilateral, nonmetastatic favorable histology (FH) Wilms tumor will survive relapse-free for four years after diagnosis, many following a treatment plan which does not include abdominal irradiation and only vincristine and actinomycin D as the chemotherapeutic agents [1–3].

Children who present with pulmonary and/or hepatic metastases from a favorable histology Wilms tumor have a less favorable prognosis. Although some children die from tumor progression, others die as the result of pneumonitis related to immunosuppression and/or radiation therapy toxicity [4]. Others die as the result of drug-induced cardiomyopathy [5].

The present study was undertaken to evaluate the efficacy and toxicity of the treatment of children with stage IV/favorable histology Wilms tumor on National Wilms Tumor Study (NWTS)-2 and 3 to increase our under-

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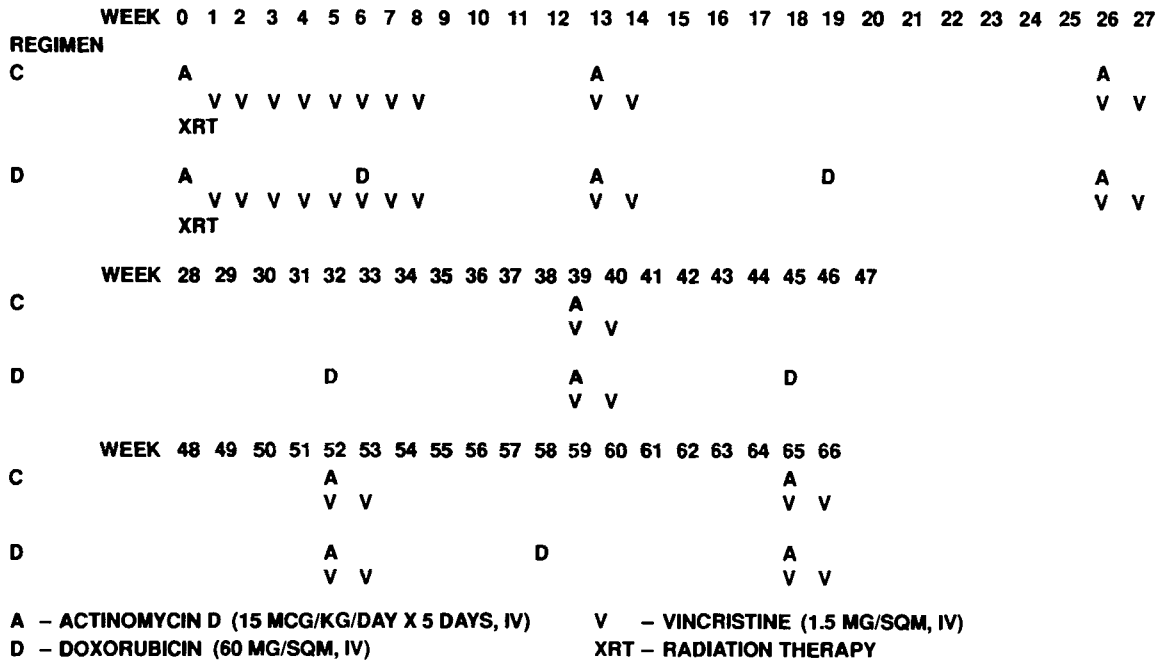

Fig. 1. Treatment randomization in National Wilms Tumor Study-2 for children with stages II–IV Wilms tumor.

standing of those factors which predict long-term survival of such patients.

Patients and Methods

National Wilms Tumor Studies-2 and 3 were multi-institutional randomized clinical trials of different treatment regimens for patients who were less than 16 years of age at diagnosis, and who were diagnosed with Wilms tumor. Stage IV patients were randomized to therapy on NWTS-2 between January 1, 1974 and July 15, 1978, and on NWTS-3 between October 1, 1979 and August 1, 1986. The grouping/staging of patients in the NWTS and the designation of patients as randomized or followed has been discussed previously [2,3] and the overall results of NWTS-2 and 3 have been previously reported [2,3]. Patients with pulmonary metastases identified only on a computed tomographic scan of the chest were excluded from the present analysis.

Patients on National Wilms Tumor Study-2 received age-adjusted abdominal radiation therapy doses (0–18 months:1,800–2,400 cGy; 19–30 months:2,400–3,000 cGy; 31–40 months:3,000–3,500 cGy; and ≥ 41 months: 3,500–4,000 cGy) and 1,400 cGy whole lung radiation therapy (Fig. 1). Patient on National Wilms Tumor Study-3 received 2,000 cGy abdominal radiation therapy and 1,200 cGy whole lung radiation therapy. The chemotherapy regimens included vincristine (VCR) + actinomycin D (AMD; regimen C), VCR + AMD + doxorubicin (DOX; regimen D and DD-RT) and VCR + AMD + DOX + cyclophosphamide (regimen J) (Fig. 2).

The flow sheets, radiation therapy summaries, lung biopsy reports and radiology reports were reviewed for all randomized patients. All deaths were reviewed by one of us (D.M.G.) to determine if death was due to disease progression, infection (pulmonary, systemic), cardiomyopathy or interstitial pneumonitis of unknown etiology. The whole lung radiation dose and the dose given to smaller ("boost") fields was determined by review of flow sheets and radiation therapy summaries.

The data were analyzed using standard statistical methods, including product limit estimates of survival curves and the log rank test [6,7].

RESULTS

Fifteen patients with stage IV/favorable histology Wilms tumor were randomized in NWTS-2 to regimen C and 26 patients to regimen D. The sites of metastases are shown in Table I. The four-year, relapse-free survival percentages were 53.3% for those on regimen C and 57.5% for those on regimen D ($P = 0.63$). The four-year survival rates were 53.3% for those on regimen C and 61.5% for those on regimen D ($P = 0.62$).

Six patients treated with regimen C developed progressive or recurrent Wilms tumor and one patient died from treatment-related toxicity. The sites of disease progression or recurrence were: pelvis–two patients; multi-

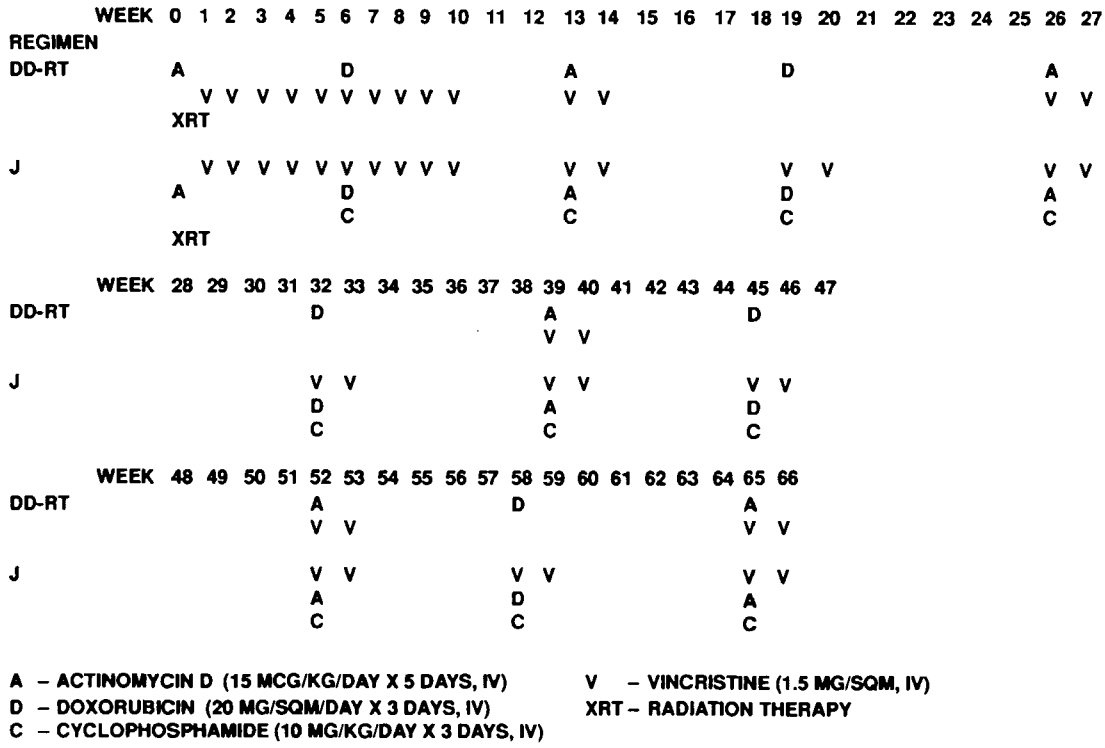

Fig. 2. Treatment randomization in National Wilms Tumor Study-3 for children with stage IV/favorable histology Wilms tumor.

TABLE I. National Wilms Tumor Study-3 Distribution of Sites(s) of Metastases

	NWTS-2		NWTS-3	
	Regimen C	Regimen D	Regimen DD-RT	Regimen J
Lung only	15	22	54	59
Liver only	0	1	2	2
Lung and liver	0	1	7	6
Other	0	2	4	2
Total	15	26	67	69

ple intraabdominal sites–one patient; and lung–three patients. One patient died from diffuse interstitial pneumonitis.

Eight patients treated with regimen D developed progressive or recurrent Wilms tumor and four patients died from treatment-related toxicity. The sites of disease progression or recurrence were: pelvis–one patient; liver–one patient; lung–six patients. The treatment-related deaths were due to: pneumocystis carinii pneumonitis–one patient; doxorubicin cardiomyopathy–one patient; gastrointestinal hemorrhage secondary to portal hypertension–one patient; and drug/radiation hepatitis and fungal sepsis–one patient.

Sixty-seven randomized patients with stage IV/favorable histology Wilms tumor in NWTS-3 were treated with regimen DD-RT and 69 patients with regimen J. The sites of metastases are shown in Table I. The four-year, relapse-free survival percentages were 79.0% for those on regimen DD-RT and 80.9% for those on regimen J ($P = 0.79$). The four-year survival percentages were 81.6% for those on regimen DD-RT and 85.3% for those on regimen J ($P = 0.87$). The four-year, relapse-free survival and overall survival percentages did not differ for patients with metastases limited to the lungs, the liver, the lungs and liver or other sites (data not shown).

Eleven patients treated with regimen DD-RT developed progressive or recurrent Wilms tumor and three patients died from treatment-related toxicity. The sites of disease progression or recurrence were: liver, peritoneum, lung–one patient; pelvis and lung–one patient; and lung only–nine patients. The treatment-related deaths were due to: drug/radiation hepatic necrosis, renal failure–one patient; and diffuse interstitial pneumonitis–two patients.

Nine patients treated with regimen J developed progressive or recurrent Wilms tumor and four patients died from treatment-related toxicity. The sites of disease progression or recurrence were: other extra-abdominal site–one patient; contralateral kidney–one patient; lung, liver and operative bed–one patient; and lung only–six patients. The treatment-related deaths were due to: diffuse interstitial pneumonitis–three patients.

The four-year, relapse-free and overall survival percentages for randomized patients with lung metastases only treated on NWTS-2 with regimen D were 54.5% and 59.1%, and for similar patients treated on NWTS-3 with regimen DD-RT were 76.6% and 81.1%. The differences between the four-year relapse-free survival percentages ($P = 0.03$) and four-year survival percentages ($P = 0.02$) were both statistically significant.

DISCUSSION

The present study was undertaken to evaluate the prognosis of patients with stage IV/favorable histology Wilms tumor entered on National Wilms Tumor Studies-2 and 3, a group of patients known to have a significant risk of treatment-related morbidity and mortality [2,4].

Patients with stage IV disease of any histological type were randomized on NWTS-2 to treatment with two drugs (VCR + AMD) or three drugs (VCR + AMD + DOX). The aggregated results for this randomization suggested that there was a marginal improvement in relapse-free survival among patients treated with three drugs ($P = 0.07$) [2]. The present analysis includes prolonged follow-up of this original cohort of patients, and was restricted to those with favorable histology. In this subgroup, there was no statistical evidence that the addition of DOX improved the relapse-free survival percentage.

Patients with stage IV disease of any histological type were randomized in NWTS-3 to treatment with three drugs (VCR + AMD + DOX) or four drugs (VCR + AMD + DOX + CTX). The initial report of this trial showed no significant difference in relapse-free survival of patients treated with three, compared to four drugs. The present analysis confirms this observation, with substantial additional follow-up.

The relapse-free survival percentage of those patients with stage IV/favorable histology Wilms tumor treated with regimen D on National Wilms Tumor Study-2 was significantly lower than that of similar patients treated with regimen DD-RT on NWTS-3. The comparison between the results of NWTS-2 and NWTS-3 must be interpreted with caution because the comparison involves the use of historical, rather than concurrently enrolled, controls. Such comparisons are liable to both identifiable and unidentifiable biases [8–11].

The group of patients treated on NWTS-2 may have included a greater number with poor prognosis metastatic sites or there may have been an excess of toxic deaths among patients on NWTS-2. Breslow and his colleagues had previously reported, however, that the site(s) of metastases did not improve or worsen the prognosis of patients with stage IV/favorable histology Wilms tumor [12]. Evaluation of the frequency of patients with various metastatic sites confirmed that there was no difference in the distribution of metastatic sites among patients treated with regimen D, compared to DD-RT.

Interstitial pneumonitis was a significant cause of morbidity and mortality among patients with stage IV Wilms tumor treated on NWTS-3 [4]. We reviewed the causes of death of all patients included in the present analysis. Death due to toxicity was more frequent among patients treated on regimen D, compared to DD-RT. Thirty-three percent of the 12 failures on regimen D were deaths due to toxicity, compared to 21% of the 14 failures on regimen DD-RT.

Others have treated children with stage IV/FH Wilms tumor, giving whole lung irradiation only to those children who do not have complete resolution of their pulmonary metastases following the first 6 weeks of treatment with a multi-drug regimen which included vincristine (1.5 mg/M^2/week × 6 weeks), actinomycin D (15 mcg/kg/day × 3 days every 3 weeks) and doxorubicin (50 mg/M^2 every 3 weeks). Postnephrectomy chemotherapy included only dactinomycin and vincristine if the local tumor stage was I. Doxorubicin was added to vincristine and dactinomycin if the local tumor stage was II or III. Dactinomycin was substituted for doxorubicin when the cumulative dose of doxorubicin reached 300 mg/M^2. The investigators of SIOP reported that the four-year, relapse-free survival percentage was 83% in 36 patients treated with prenephrectomy chemotherapy, followed by nephrectomy in a limited institution pilot study. Whole lung radiation therapy was given only to patients who did not achieve a complete remission after treatment with chemotherapy [13].

Investigators in the United Kingdom Children's Cancer Study Group (UKCCSG) conducted a similar trial. The chemotherapy regimen included vincristine (1.5 mg/M^2/week × 10 weeks, then every 3 weeks), actinomycin D (1.5 mg/M^2 every 6 weeks for one year), doxorubicin (40 mg/M^2 every 6 weeks for one year) and cyclophosphamide (600 mg/M^2 every 3 weeks, with the doses of dactinomycin or doxorubicin). The cumulative doxorubicin dose was 360 mg/M^2. The six-year survival percentage was 65% [14], compared to 81.6% for similar patients entered on NWTS-3. The results of both the SIOP and UKCCSG studies suggest that a significant proportion of patients with stage IV/favorable histology Wilms tumor may be treated successfully without the use of whole lung radiation therapy if the chemotherapy regimen includes an anthracycline.

Doxorubicin was administered in NWTS-2 and NWTS-3 using different schedules. In NWTS-2 doxorubicin was given as a single dose of 60 mg/M^2, and on NWTS-3 doxorubicin was administered using the schedule of 20 mg/M^2/day × 3 days. The toxicity results would be consistent with an effect of schedule on toxicity, with the single dose producing greater toxicity.

The superior relapse-free survival results observed with regimen DD-RT would be consistent with an effect of dose schedule on treatment efficacy, with the divided dose schedule of DOX possibly being therapeutically superior, although proof of such an effect would require a randomized clinical trial. There was no evidence that the combined group of patients with group II (lymph node-positive) and group III (excluding those with spill limited to the flank)/FH Wilms tumor treated on NWTS-2 with regimen D had inferior relapse-free survival compared to those with stage III/FH Wilms tumor treated on NWTS-3 with regimen DD-RT (unpublished data). The differences in relapse-free and overall survival of patients treated with regimens D and DD-RT would also be consistent with an effect of increased physician experience with administration of and managing the complications of combined modality therapy.

The results of this analysis suggest that approximately one-half of all children with stage IV/FH Wilms tumor can be treated successfully without exposure to an anthracycline if their treatment protocol includes whole lung radiation therapy. The results of NWTS-3, in which patients with stages II or III/favorable histology Wilms tumor, treated with an intensified regimen which included dactinomycin and vincristine, had relapse-free and overall survival percentages which did not differ significantly from those of patients treated with a three-drug regimen which included vincristine, dactinomycin and doxorubicin, support this suggestion [3]. Because this group of patients is at substantial risk of anthracycline-associated cardiomyopathy as the result of drug exposure and cardiac irradiation [5], and anthracycline-related leukemogenesis [15–17] and carcinogenesis [18], the ability to identify this subgroup at the time of initial diagnosis would allow the subgroup who derive no benefit from anthracycline therapy to be spared the potential long-term morbidity of such treatment. Preliminary data suggest that loss of heterozygosity at 16q in tumor tissue may identify patients with a poor prognosis [19]. The goal of future research will be the confirmation of these laboratory observations which may facilitate the identification of this subgroup and those in other stages who can be managed successfully using less intensive treatment regimens. More intensive chemotherapy regimens, employing one or more of several active agents, such as etoposide and/or carboplatin, could be evaluated in those whose biological prognostic factors suggest an unfavorable prognosis [20].

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